Registration Decision RD2015-27

Benzovindiflupyr

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Registration Decision for Benzovindiflupyr

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, is proposing full registration for the sale and use of Benzovindiflupyr Technical, A15457 TO Fungicide and Aprovia, containing the technical grade active ingredient benzovindiflupyr, to control fungal diseases in turf, ornamentals and several food crops. Also proposed for registration are several end use products formulated with benzovindiflupyr and currently registered fungicides. These products are formulated with azoxystrobin (Mural Fungicide and Elatus), propiconazole (A18933 Fungicide), difenoconazole (Aprovia Top and Ascernity Fungicide) and fludioxonil (Instrata II Fungicide).

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

These products were first proposed for registration in the consultation document[1] Proposed Registration Decision PRD2015-07, *Benzovindiflupyr*. This Registration Decision[2] describes this stage of the PMRA's regulatory process for benzovindiflupyr and summarizes the Agency's decision, the reasons for it and provides, in Appendix I, a summary of comments received during the consultation process as well as the PMRA's response to these comments. This decision is consistent with the proposed registration decision stated in PRD2015-07.

For more details on the information presented in this Registration Decision, please refer to the Proposed Registration Decision PRD2015-07, *Benzovindiflupyr* that contains a detailed evaluation of the information submitted in support of this registration.

What Does Health Canada Consider When Making a Registration Decision?

The key objective of the *Pest Control Products Act* is to prevent unacceptable risks to people and the environment from the use of pest control products. Health or environmental risk is considered acceptable[3] if there is reasonable certainty that no harm to human health, future generations or the environment will result from use or exposure to the product under its conditions of registration. The Act also requires that products have value[4] when used according to label directions. Conditions of registration may include special precautionary measures on the product label to further reduce risk.

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1 "Consultation statement" as required by subsection 28(2) of the *Pest Control Products Act*.

2 "Decision statement" as required by subsection 28(5) of the *Pest Control Products Act*.

3 "Acceptable risks" as defined by subsection 2(2) of *Pest Control Products Act*.

4 "Value" as defined by subsection 2(1) of *Pest Control Products Act* "... the product's actual or potential contribution to pest management, taking into account its conditions or proposed conditions of registration, and includes the product's (*a*) efficacy; (*b*) effect on host organisms in connection with which it is intended to be used; and (*c*) health, safety and environmental benefits and social and economic impact".

To reach its decisions, the PMRA applies modern, rigorous risk-assessment methods and policies. These methods consider the unique characteristics of sensitive subpopulations in humans (for example, children) as well as organisms in the environment (for example, those most sensitive to environmental contaminants). These methods and policies also consider the nature of the effects observed and the uncertainties when predicting the impact of pesticides. For more information on how the PMRA regulates pesticides, the assessment process and risk-reduction programs, please visit the Pesticides and Pest Management portion of Health Canada's website at healthcanada.gc.ca/pmra.

What is Benzovindiflupyr?

Benzovindiflupyr is a member of the succinate-dehydrogenase inhibitors (SDHI) class of fungicides, which acts on target pathogens by interfering with the normal respiration process in fungal cells. This fungicidal active ingredient is intended for application alone or in combination with other active ingredients with different modes of action to provide broad spectrum control or suppression of important plant diseases.

Health Considerations

Can Approved Uses of Benzovindiflupyr Affect Human Health?

Products containing benzovindiflupyr are unlikely to affect your health when used according to label directions.

Potential exposure to benzovindiflupyr may occur through the diet (food and water), when handling and applying end-use products containing benzovindiflupyr or when exposed to treated areas. When assessing health risks, two key factors are considered: the levels where no health effects occur and the levels to which people may be exposed. The dose levels used to assess risks are established to protect the most sensitive human population (for example, children and nursing mothers). Only uses for which the exposure is well below levels that cause no effects in animal testing are considered acceptable for registration.

Toxicology studies in laboratory animals describe potential health effects from varying levels of exposure to a chemical and identify the dose where no effects are observed. The health effects noted in animals occur at doses more than 100-times higher (and often much higher) than levels to which humans are normally exposed when benzovindiflupyr products are used according to label directions.

In laboratory animals, the technical grade active ingredient benzovindiflupyr was of high acute toxicity by the oral route, low dermal toxicity and slightly acutely toxic via the inhalation route. Benzovindiflupyr was minimally irritating to the eyes and skin. It did not cause an allergic skin reaction. Based on these findings, the signal word and hazard statements "DANGER – POISON" are required on the label.

There are several end-use products containing benzovindiflupyr. Aprovia, also known as A15457B and A15457TO, containing benzovindiflupyr was moderately acutely toxic via the oral route and slightly acutely toxic via the inhalation route. It was of low acute dermal toxicity. It was considered corrosive to the eyes and was severely irritating to the skin, but did not cause an allergic skin reaction. Based on these findings, the signal word and hazard statements "POISON" and "DANGER – CORROSIVE TO EYES AND SKIN" are required on the product label.

Elatus, also known as A18126B, containing benzovindiflupyr and azoxystrobin was slightly acutely toxic via the oral route and of low acute toxicity via the dermal and inhalation routes. It was moderately irritating to the eyes, non-irritating to the skin and caused an allergic skin reaction. Based on these findings, the signal word and hazard statements "POISON", "WARNING – EYE IRRITANT" and "POTENTIAL SKIN SENSITIZER" are required on the product label.

The end-use product A18993A, containing benzovindiflupyr and propiconazole was moderately acutely toxic via the oral route, slightly acutely toxic via the inhalation route, and was of low acute dermal toxicity. It was severely irritating to the eyes and mildly irritating to the skin, but did not cause an allergic skin reaction. Based on these findings, the signal word and hazard statements "POISON" and "DANGER –EYE AND SKIN IRRITANT" are required on the product label.

The acute toxicity of the end-use product Aprovia Top, also known as A19334A, containing benzovindiflupyr and difenoconazole was slightly acutely toxic via the oral and inhalation routes and of low acute toxicity via the dermal route. It was severely irritating to the eyes, slightly irritating to the skin and did not cause an allergic skin reaction. Based on these findings, the signal word and hazard statements "POISON" and "DANGER –EYE IRRITANT" are required on the product label.

Ascernity, also known as A19188A, containing benzovindiflupyr and difenoconazole was slightly acutely toxic via the oral route and of low acute toxicity via the dermal and inhalation routes. It was moderately irritating to the eyes, but non-irritating to the skin and did not cause an allergic skin reaction. Based on these findings, the signal word and hazard statements "POISON" and "WARNING –EYE IRRITANT" are required on the product label.

Health effects in animals given repeated doses of technical benzovindiflupyr primarily involved decreased body weight and body weight gain, effects on the liver, along with indications of general toxicity. There was no indication that benzovindiflupyr caused damage to the immune system. Benzovindiflupyr did not cause birth defects in animals. There was no evidence to suggest that benzovindiflupyr damaged genetic material. Benzovindiflupyr did, however, cause thyroid tumors in male rats following prolonged dosing.

When benzovindiflupyr was given to pregnant or nursing animals, no effects on the developing fetus or juvenile animal were observed at doses that were toxic to the mother, indicating that the young do not appear to be more sensitive to benzovindiflupyr than the adult animal.

The risk assessment protects against the effects of benzovindiflupyr by ensuring that the level of human exposure is well below the lowest dose at which these effects occurred in animal tests.

Residues in Water and Food

Dietary risks from food and drinking water are not of health concern.

Aggregate dietary intake estimates (food plus drinking water) revealed that the general population and children 1-2 years old, the subpopulation which would ingest the most benzovindiflupyr relative to body weight, are expected to be exposed to less than 3% of the acceptable daily intake. Based on these estimates, the chronic dietary risk from benzovindiflupyr is not of health concern for all population subgroups.

A threshold approach was taken for the cancer risk assessment. The toxicological endpoints selected for chronic dietary risk assessment are considered to be protective of these findings. There is no lifetime cancer risk from the use of benzovindiflupyr.

Acute dietary (food plus drinking water) intake estimates for the general population and all population subgroups were less than or equal to 9% of the acute reference dose, and are not of health concern.

The *Food and Drugs Act* prohibits the sale of adulterated food, that is, food containing a pesticide residue that exceeds the established maximum residue limit (MRL). Pesticide MRLs are established for *Food and Drugs Act* purposes through the evaluation of scientific data under the *Pest Control Products Act*. Food containing a pesticide residue that does not exceed the established MRL does not pose an unacceptable health risk.

Residue trials conducted throughout Canada and the United States using benzovindiflupyr on pome fruit, grapes, potatoes, fruiting vegetables, cucurbits, dry peas and beans, soybeans, cereals, cotton, peanuts and canola are acceptable. For imported sugarcane, residue trials conducted in Brazil are acceptable. The MRLs for this active ingredient can be found in the Science Evaluation of this Consultation Document.

Risks in Residential and Other Non-Occupational Environments

Non-occupational risks are not of concern when products containing benzovindiflupyr are used according to the label directions.

Adults and youth may be exposed to benzovindiflupyr while golfing on treated courses. Based on the expected short to intermediate term duration of this activity, risk to golfers is not a concern.

Adults, youth and toddlers may be exposed to benzovindiflupyr during pick-your-own harvesting activities. Based on the expected acute term duration of these activities, risk to the general population is not of concern.

Occupational Risks From Handling Benzovindiflupyr

Occupational risks are not of concern when products containing benzovindiflupyr are used according to the label directions, which include protective measures.

Farmers and custom applicators who mix, load or apply products containing benzovindiflupyr as well as field workers re-entering freshly treated fields, turf, nurseries and greenhouses can come in direct contact with benzovindiflupyr residues on the skin. Therefore, the label specifies that anyone mixing/loading and applying products containing benzovindiflupyr must wear a long-sleeved shirt and long pants, chemical-resistant gloves, and goggles when mixing, loading and applying or during equipment clean-up or repair. Goggles and chemical-resistant gloves are not required during groundboom application or closed-cab applications. For A15457TO Fungicide and Aprovia, an additional layer of clothing is required due to acute skin irritation potential. The label also requires that workers do not enter treated fields for 12 hours after application for agricultural applications except for girdling and turning in grapes, which requires a 4 day restricted-entry interval (REI). For golf course turf applications, an REI of "until residues have dried" is required. Taking into consideration these label statements, the number of applications and the expectation of the exposure period for handlers and workers, the risk from exposure to benzovindiflupyr for these individuals is not a concern.

For bystanders, exposure is expected to be much less than that for workers and is considered negligible. Therefore, health risks to bystanders are not of concern.

Environmental Considerations

What Happens When Benzovindiflupyr is Introduced into the Environment?

When used according to label directions, benzovindiflupyr does not pose an unacceptable risk to the environment.

Benzovindiflupyr can enter the environment when it is used for the control of fungal diseases on a variety of agricultural food crops, on outdoor ornamental plants and on turf. It can be applied by foliar spray application, and by soil application (in furrow treatment of soil before planting root vegetables). Environmental exposure is considered limited when benzovindiflupyr is used as a fungicide in greenhouses.

In the terrestrial environment, benzovindiflupyr breaks down very slowly and has the potential to carryover from one growing season to the next. Breakdown of the molecule occurs mainly through soil microbial activities which produce only minor transformation products. Benzovindiflupyr is considered to have low potential to move through the soil to enter groundwater. However, it does have the potential to enter aquatic environment through surface run-off and spray-drift.

In the aquatic environment, benzovindiflupyr is broken down slowly by microorganisms. Once benzovindiflupyr enters the aquatic environment, it tends to move from the water layer to the sediment layer, where it may persist for multiple years.

Benzovindiflupyr is not expected to accumulate in the tissues of organisms.

Benzovindiflupyr and its minor transformation products present a negligible risk to earthworms, to pollinators and to aquatic sediment-dwelling invertebrates. At high enough concentrations,benzovindiflupyr may pose a risk to terrestrial vascular plants and to certain aquatic organisms (freshwater and marine invertebrates, amphibians). To minimize exposure to non-target organisms, spray buffer zones are required to protect terrestrial, freshwater and estuarine/marine habitats adjacent to areas treated with benzovindiflupyr. Toxicity statements are also required on the product label for terrestrial plants and aquatic organisms.

Value Considerations

What Is the Value of Aprovia, A15457TO Fungicide, Elatus, A18993 Fungicide, Aprovia Top, Mural Fungicide, Ascernity Fungicide, and Instrata II Fungicide

Aprovia and A15457TO Fungicide

Benzovindiflupyr, the active ingredient in Aprovia and A15457TO Fungicide, controls or suppresses economically important diseases of food crops, turf and ornamentals.

Both Aprovia and A15457TO Fungicide contain 100 g/L benzovindiflupyr. Aprovia is applied as a foliar treatment against fungal diseases of food crops, while A15457TO Fungicide is applied as a foliar treatment against certain diseases in turf, greenhouse ornamentals and outdoor ornamentals.

Elatus and Mural Fungicide

Benzovindiflupyr and azoxystrobin, the active ingredients in Elatus and Mural Fungicide, control or suppress economically important diseases of food crops and ornamentals.

Both Elatus and Mural Fungicide contain 15% benzovindiflupyr and 30% azoxystrobin. Elatus is applied as a foliar treatment against fungal diseases of food crops, while Mural Fungicide is applied as a foliar treatment against certain diseases in greenhouse and outdoor ornamentals.

A18993 Fungicide

Benzovindiflupyr and propiconazole, the active ingredients in A18993 Fungicide, control economically important diseases of food crops.

A18993 Fungicide, containing 75 g/L benzovindiflupyr and 125 g/L propiconazole, is applied as a foliar treatment against fungal diseases of food crops.

Aprovia Top and Ascernity Fungicide

Benzovindiflupyr and difenoconazole, the active ingredients in Aprovia Top and Ascernity Fungicide, control or suppress economically important diseases of food crops and turf.

Aprovia Top, containing 78 g/L benzovindiflupyr and 117 g/L difenoconazole, is applied as a foliar treatment against fungal diseases of food crops; while Ascernity Fungicide, containing 24 g/L benzovindiflupyr and 79 g/L difenoconazole, is applied as a foliar treatment against certain diseases of turf.

Instrata II Fungicide

Instrata II Fungicide is a tankmix combination package consisting of Instrata II A (containing 24 g/L benzovindiflupyr and 79 g/L difenoconazole) and Instrata II B (containing125 g/L fludioxonil). As a treatment for golf course turf, the tankmix combination will provide control of pink and grey snow mold through the combined activity of three different fungicidal modes of action.

Measures to Minimize Risk

Labels of registered pesticide products include specific instructions for use. Directions include risk-reduction measures to protect human and environmental health. These directions must be followed by law.

The key risk-reduction measures being proposed on the label of Mural Fungicide, Elatus, A18933 Fungicide, Aprovia Top Fungicide, Ascernity Fungicide and Instrata II Fungicide to address the potential risks identified in this assessment are as follows.

Key Risk-Reduction Measures

Human Health

Because there is a concern with users coming into direct contact with benzovindiflupyr on the skin or through inhalation of spray mists, anyone mixing/loading and applying products containing benzovindiflupyr must wear a long sleeved-shirt and long pants, chemical-resistant gloves, and goggles when mixing, loading and applying or during equipment clean-up or repair. Goggles and chemical-resistant gloves are not required during groundboom application or closed-cab applications. For A15457TO Fungicide and Aprovia, an additional layer of clothing is required due to acute skin irritation potential. The label also requires that workers do not enter treated fields for 12 hours after application for agricultural applications except for girdling and turning in grapes, which requires a 4 day restricted-entry interval (REI). For golf course turf applications, an REI of "until residues have dried" is required. In addition, standard label statements to protect against drift during application were added to the label as well as a restriction against use in residential areas.

Environment

To minimize the potential of benzovindiflupyr to be carried over to the following growing season, a label statement informing the users of the carry-over potential of this chemical is to be specified on the benzovindiflupyr end-use product labels that are specified for outdoor uses.

To mitigate potential exposure of terrestrial organisms through spray-drift, appropriate spray buffer zones are required to protect sensitive terrestrial habitats.

To mitigate potential exposure of aquatic organisms through spray-drift, appropriate spray buffer zones are required to protect sensitive aquatic habitats.

Other Information

The relevant test data on which the decision is based (as referenced in PRD2015-07, *Benzovindiflupyr*) are available for public inspection, upon application, in the PMRA's Reading Room (located in Ottawa). For more information, please contact the PMRA's Pest Management Information Service by phone (1-800-267-6315) or by e-mail (pmra.infoserv@hc-sc.gc.ca).

Any person may file a notice of objection[5] regarding this registration decision within 60 days from the date of publication of this Registration Decision. For more information regarding the basis for objecting (which must be based on scientific grounds), please refer to the Pesticides and Pest Management portion of the Health Canada's website (Request a Reconsideration of Decision) or contact the PMRA's Pest Management Information Service.

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5 As per subsection 35(1) of the *Pest Control Products Act*.

Appendix I Comments and Responses

1. Comment: Page 19 Section 3.1 – In the paragraph beginning, "*A limited battery*", SYN546039 is also known as CSCD695908 (not CSD695909) as indicated on the Certificate of Analysis included with studies 2255491 and 2255492. It is not clear what is meant by "DF-pyrazole" and this appears to refer to the AMES study submitted for CA4312 which is also CSAA798670 and NOA449410.

Response: In the AMES test, (PMRA #2255385, Report Number 1077403), entitled "CA4312 – Salmonella Typhimurium and Escherichia Coli Reverse Mutation Assay with DF-pyrazole acid," both CA4312 and DF-pyrazole were used interchangeably. PMRA agrees with the following clarifications and corrections to the text:

"A limited battery of tests was performed on a number of metabolites. CSCD465008, also known as R9548945 or SYN545720, is a metabolite found in plants and soil. It was of low acute oral toxicity and was negative in genotoxicity studies. SYN546039, also known as CSCD695908, is found in rats, plants, soil and surface water and was of low acute oral toxicity and was negative in an Ames test. CSAA798670, also known as NOA449410, CA4312, DF-pyrazole acid and R648993, was found in plants, soil and water and was negative in genotoxicity tests and produced no signs of toxicity in a 28-day oral toxicity study in rats up to the limit dose. Metabolites SYN546482 and NOA449109 although not specified as to origin, were negative in an Ames test."

2. Comment: Page 64 -TABLE 3. In the sentence "An i.v. pharmacokinetics assay indicates that oral absorption is essentially complete at 1 mg/kg bw" there is a confusion of terms. The iv study allowed the comparison with oral dosing and the determination of oral bioavailability not oral absorption as mentioned above. The oral studies indicated oral absorption.

Response: PMRA agrees with the text "Comparison to the i.v. pharmacokinetics assay indicates that oral absorption is essentially complete at 1 mg/kg bw".

3. Comment: Page 64 – TABLE 3. In the sentence "T1/2 elim values after repeat dosing were between 2.49 days in the plasma and 26.19, 49.59, 61.77 and 69.06 days in the renal fat, brain, thymus and testes, respectively ", the correct value for renal fat is 36.19.

Response: PMRA agrees the correct value for the renal fat is 36.19.

4. Comment: Page 67 – Table 3. Regarding the statement in the table in Appendix I, 104 W Dietary Wistar Rat "Evidence of carcinogenicity" it would be helpful to provide context such as, "Not relevant for human risk assessment".

Response: As this comment refers to the row of Table 3 dedicated to the rat chronic and combined toxicity study, reference to the relevance to human risk assessment is not appropriate. Context, as requested, occurs in Sections 3.1, 3.3 and the last row of Table 4.

5. Comment: Page 70- Please verify based on Lake 2002 that 28 is correct and not 14 in the following statement, "…28 days for 3 of 4 expressions, ↑ UDPGT activity towards thyroxine as substrate after 28 days expressed as per relative liver weight only".

Response: This section of the table refers to Robertson 2010 (report number 300006), therefore, 28 days is correct.

6. Comment: Page 70 - Based on Lake 2002 the impact of phenobarbital was only assessed at Day 7 therefore the following statement is not accurate: "…↑ UDPGT activity towards thyroxine as substrate after 3, 7 and 28 days for all expression."

Response: PMRA agrees with the text "after 7 days for all expressions"